

EXHIBIT 65

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Modified-Release Opioid Risk Management Program: Safety Overview

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What Is a Risk Management Program?

- A Risk Management Program (RMP) is a program of activities designed to
 - Minimize the risks associated with medications
 - Maximize the benefits of medications
 - Ensure patient safety
- Manage risk by developing *proactive* risk management strategies
- Minimize the need for *reactive* responses

Modified-Release Opioid RMP: Content Overview

■ Objectives

- Estimate and evaluate risk
- Manage known risks associated with a drug
- Optimize risk/benefit ratio
 - Balance benefits gained from the medication with potential risks
- Promote safe use of the medication
- **Protect public health**

Modified-Release Opioid RMP: Key Elements

- Risk of accidental exposure
 - Especially in modified-release products with large amounts of opioid
- Risk of improper patient selection
 - Who are the appropriate patients?
- Risk for abuse and misuse
 - How can we reduce risk for patients and the community?

Modified-Release Opioid RMP: Content Overview

- Endo's RMP
 - Minimize misuse/abuse and diversion of opioids via the components of RM
 - Risk Assessment
 - Risk Management/Intervention
 - Risk Communication/Education

Risk Assessment

- Challenges of risk assessment:
 - How prevalent is abuse/diversion?
 - Absence of good data
 - Spectrum of populations
 - Acute pain pts? Chronic pain pts? Addicts?
 - Background rates?
 - How to assess potential for abuse/misuse?
 - Lack of well-validated tools, yet
 - **NEED** to assess relative risk of aberrant behaviors

S.O.A.P.P

Screener and Opioid Assessment for Patients with Pain

- 1st prospectively-validated opioid assessment screener
 - Being developed under NIDA/NIH grant to Inflexxion
- Practical tool to help predict relative potential to misuse opioid medications
 - Addiction, diversion, recreational use
- For use in pts being considered for long-term opioid tx
 - Purpose is **NOT** to deny pts access to pain medication
 - Purpose is **NOT** to “screen in” or “screen out”
- Purpose **IS** to assist clinician in deciding:
 - Level of monitoring a given patient may require
 - If multidisciplinary or pain consult would be useful
 - Help document decisions

S.O.A.P.P

Screener and **O**pioid **A**ssessment for **P**atients with **P**ain

- Brief, self-report screener
 - 5-10 minutes for patient to complete
- SOAPP version I
 - Naturalistic observation / Concept mapping / Expert consensus
 - Face valid / intuitive
 - 24-items / Likert-like response scale (0 to 4)
 - Pilot study in 154 pts at Brigham & Women's showed reliability & predictive validity of scale
- SOAPP version II
 - Empirically-derived
 - Predictive validity (via prospective study)

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Back Forward Stop Home Search Favorites Media

Address http://inflexx-devil/PainEDU_2004/soap.asp?UserID=0

PainEDU.org

IMPROVING PAIN TREATMENT THROUGH EDUCATION

E-MAIL ADDRESS

PASSWORD

FORGOT YOUR PASSWORD?

NOT REGISTERED?

PAINEDU COURSE SPOTLIGHT ROUNDTABLE BOOK REVIEWS TOOLS POPULATIONS NEWS AND RESOURCES



SOAPP

Access an important tool that helps predict patient response to opioid medications.

DOWNLOAD THE SOAPP

Download a free copy of the SOAPP tool and SOAPP Monitoring Recommendations.

[Click for more](#)

CONTACT THE SOAPP TEAM

E-mail us any questions about the tool or to share your impressions of the SOAPP tool.

[Click for more](#)

ABOUT THE SOAPP

The **S**creener and **O**pioid **A**ssessment for **P**atients in **P**ain (SOAPP) is a tool to facilitate treatment planning for chronic pain patients being considered for long-term opioid treatment.

SOAPP version 1.0 is:

- ✓ A 24 item paper and pencil questionnaire
- ✓ Takes < 10 minutes to complete and simple to score
- ✓ Developed based on expert consensus
- ✓ Ideal for documenting decisions about the level of monitoring planned for a particular patient or justifying referrals to specialty pain clinic.
- ✓ View [hyperlink to SOAPP development] preliminary reliability and validity data

Learn more about the **SOAPP** tool. [Link icon](#)

Utility in Clinical Practice

- **NEED** to assure SOAPP can be readily integrated into clinical practice
- **NEED** to assure SOAPP is not used:
 - To deny pts access to pain medications
 - To supplant clinical judgement
- Background & instructions at www.painedu.org
- Diffusion/delivery system testing
 - Paper/pencil questionnaire
 - Electronic/PDA
 - IVR (interactive voice recognition)
 - Web-based
 - Fax back

COMM: **C**urrent **O**pioid **M**isuse **M**easure

- Brief screener to help identify misuse in chronic pain pts who are already on opioid therapy
- Clinician checklist based upon input from 26 pain & addiction specialists
- Anticipated benefits:
 - Improved ongoing assessment of pts on chronic opioid therapy
 - Improved risk management & tx decision making
- Completed 2/04, but not yet validated

Modified-Release Opioid RMP: Risk Assessment

- Safety surveillance
 - Trending
 - Signal detection
- Key elements
 - Postmarketing surveillance
 - ESRB-Endo Safety Review Board
 - Risk Management Team
 - Media screening

Post Marketing Safety Surveillance Program (cont)

- On-going monitoring & evaluation of adverse events received from spontaneous reports
- Monitoring & evaluation of adverse events in on-going clinical trials for signals & trends

Post Marketing Safety Surveillance Program: ESRB

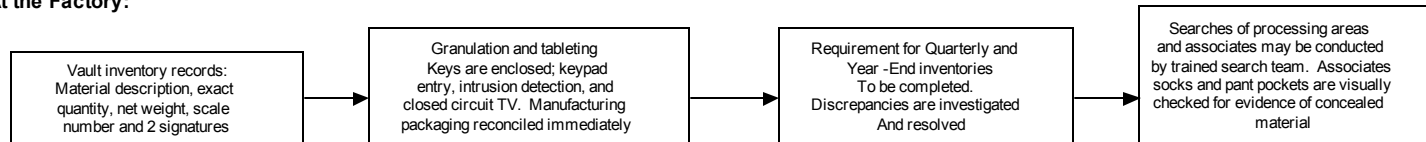
- Multi-disciplinary Safety Review Board
 - Meets quarterly
 - Reviews post-marketing safety data collected on oxymorphone ER/IR
 - Investigates and reviews all cases of drug abuse/misuse, drug dependence and drug overdose to detect trends
 - Comparison of oxymorphone adverse event profile with other opioids via the FDA's Freedom of Information Act

Post Marketing Safety Surveillance Program

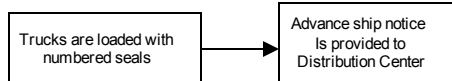
- Risk Management Team
 - Internal multidisciplinary team
 - Expert advisors with safety, epidemiology, opioid, pain, and addiction medicine backgrounds
 - Monitoring nationally recognized databases such as DAWN
 - Media Surveillance
- Analysis of data
 - Stratification by events, geographic area, and age

Endo Safeguards to Prevent Opioid Diversion

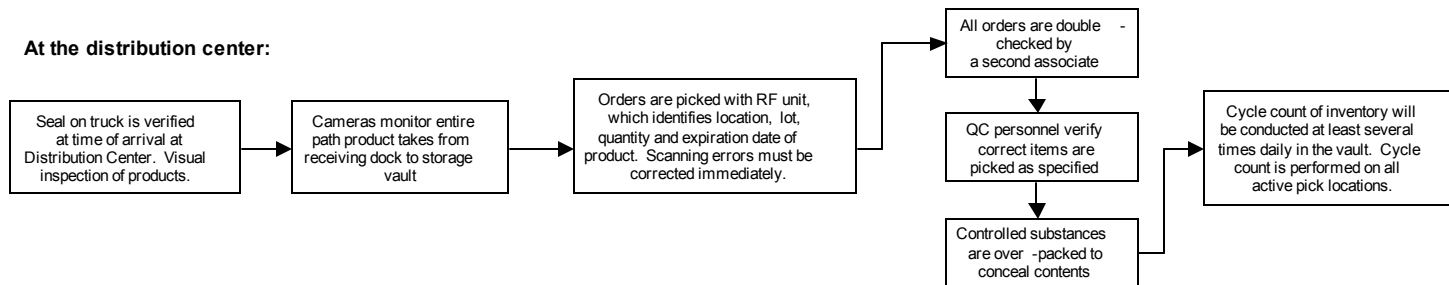
At the Factory:



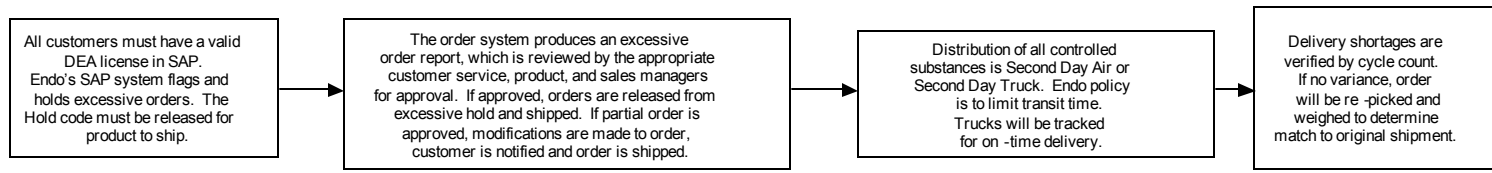
In transit to the distribution center:



At the distribution center:



To the wholesale distributor, institution, or pharmacy:



Modified-Release Opioid RMP: Risk Communication

- Proactive risk communication
 - Education/ CME
 - “Dear Health Care Provider” letters
 - Patient brochures
 - Product labeling
 - Appropriate training of sales representatives
 - Partnering with professional societies

Appropriate Training of Sales Representatives

- Messages on label with respect to:
 - Appropriate patient selection
 - Appropriate use of oxymorphone ER/IR
- Serve as an educational resource
 - Advocate **responsible** pain mgmt
 - Provide access to validated assessment and patient management tools
 - Provide **balanced** patient education materials

Modified-Release Opioid RMP: Risk Intervention

- Risk Intervention
 - Intervention to targeted areas
 - Increase education on risk of abuse
 - Cooperate with local law enforcement agencies, FDA, and DEA
 - Maintain tight control of supply chain



Assuring the Appropriate Use of Opioid Analgesics

Appropriate Use of Opioid Analgesics

■ Rationale

- Studies have confirmed the usefulness of opioids in the treatment of chronic pain
- While **controlled studies in chronic pain are needed**, some studies in current literature suggest:
 - relatively low incidence of misuse among **most** pts who receive opioid analgesics for pain
 - potential for increased functioning & improved quality of life
- However....

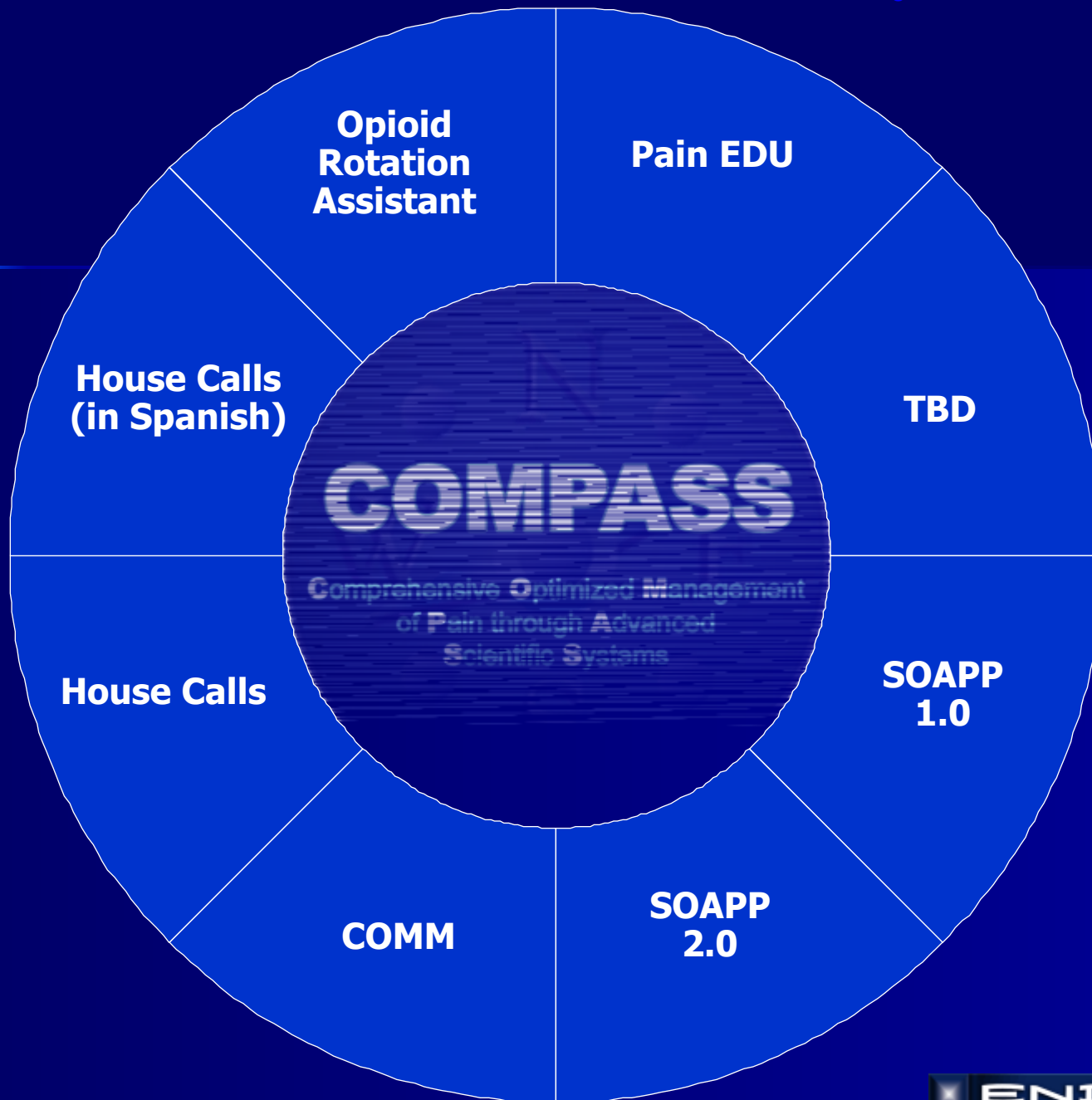
Appropriate Use of Opioid Analgesics

■ Rationale (cont'd)

- Physicians have legitimate concerns about prescribing opioids responsibly:
 - Concerns about addiction
 - Worry about possible abuse/misuse by patients (e.g., diversion and loss of control)
 - Liability and censure by regulatory agencies
 - Determining which pts are appropriate candidates for opioid therapy
 - Nat'l media attention re: abuse of prescription opioids has underscored these issues

Assuring Pain Relief While Preventing Abuse: A Critical Balancing Act

- There is a need for scientifically-balanced education addressing:
 - Principles of prescribing opioid analgesics
 - “Pharmacology 101” to optimize efficacy, reduce AE’s
 - Principles of risk assessment and management
- Endo recognizes that:
 - Access to opioid analgesics is critical to patients suffering from pain, but that
 - Risk of addiction & diversion must be addressed



Opioid Education Initiatives for Physicians

- National Initiative on Pain Control
- McGraw Hill & NIH handbooks
- Primary Care & Resident “Essentials of Pain Mgmt” courses
- AAFP, STFM, ACP, and HHS Educational Initiatives
- “Appropriate Use of Opioids” kit
 - Physician, patient & family education materials
 - Pain assessment tools
 - Prototype pain mgmt agreements & documentation templates
- Scientific Resource Center at national congresses

Opioid Education Initiatives for Pharmacists

- Critical link between physician & patient
 - Can enhance compliance, reduce risk of AE's, alert physician to any red flags
- US Pharmacist & PharmAlert publications
- APhA new product bulletins
- ASHP pain traineeship
- Symposia at annual meetings

Opioid Education Initiatives for Patients & Families

- Critical that patients/families understand both risks & benefits of opioid analgesics
- “Understanding Your Pain: Taking Oral Opioid Analgesics” booklet
- “Using a Pain Assessment Scale” brochure
- Brief Pain Inventory tear-pads
- National patient initiatives
 - APF, NPF, AACPI, ACPA
 - Dept of Health & Human Services

Partnering with Professional Societies

- AAFP
 - CE-accredited video & monograph
 - Journal of Family Practice supplement
 - support of state academy initiatives
- STFM
 - Workshops, roundtables & handbooks at annual meetings
 - Precourses at regional meetings; regional “train the trainer”
- ACP
 - core curriculum & handbooks at annual meetings
 - pocket reference guides
- PriMed
 - Symposia at regional PriMed meetings

Your Recommendations

- **Other opportunities?**
- **Unmet needs?**
- **What can actually help effect meaningful change?**